Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
ELSEVIER
Tetrahedron Letters 48 (2007) 791–794

A two-step procedure for the preparation of mono-protected bis-*N*-heterocyclic alkyl ether systems

Jianhua Chao,[a,*] Mariam Israiel,[b] Junying Zheng[a] and Cynthia Aki[a]

[a]*Schering-Plough Research Institute, Kenilworth, NJ 07033, USA*
[b]*New Jersey City University, Jersey City, NJ 07305, USA*

Received 5 November 2006; revised 21 November 2006; accepted 28 November 2006
Available online 19 December 2006

Abstract—A two-step convenient sequence for the synthesis of previously inaccessible mono-Boc-protected bis-*N*-heterocyclic alkyl substituted ether derivatives **4** is described. Mitsunobu protocol was applied to the preparation of pyridinyl ether precursor **5**. The reduction of the electron rich pyridinyl system **5** has been achieved catalytically using the combination of PtO_2–H_2SO_4 or PtO_2–*p*TsOH under a hydrogen atmosphere maintained by a gas balloon at ambient temperature.

As part of our recent medicinal chemistry efforts, we needed to make bis-*N*-heterocyclic alkyl substituted ether systems, illustrated as general formula **1** in Figure 1. A survey of the literature found no precedent for the construction of such ether systems, in spite of numerous methods for the preparation of substituted piperidines.[1,2] The underlining difficulty lies in connecting two *N*-heterocycles via an ether linkage without using harsh conditions. Only two patent applications to date have reported simple examples containing solely [6,6] bicyclic ring systems (**2** and **3**, Fig. 1), prepared through multi-step synthesis, which are intended for anti-inflammatory use (**2**)[3] or for treatment of neurological and psychiatric disorders (**3**).[4] To serve our purpose, we have developed a two-step sequence, carried out under mild conditions, that has been effective in the preparation of such ether systems (**1**) in various ring sizes. Herein, we report our results and findings.

The preparation of compound **1** could be readily achieved via the mono-protected building block **4**. We envisioned a two-step sequence to access this key intermediate (Scheme 1), by reduction of the pyridinyl–piperidyl ether precursor **5**, which could be generated from hydroxy pyridine **6** and hydroxy-*N*-heterocycle **7** utilizing the Mitsunobu protocol. With the two N-terminals properly differentiated, mono-protected bis-*N*-heterocyclic ethers **4** would allow asymmetric functionalization, thus providing uninhibited access to **1**.

Pyridinyl ethers **5** were smoothly prepared by taking advantage of the Mitsunobu reaction,[5] which offers an

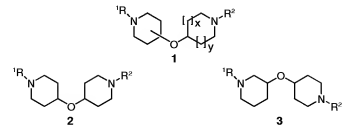
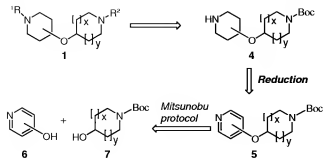


Figure 1. Bis-*N*-heterocyclic alkyl substituted ethers.

Keywords: Bis-*N*-heterocyclic alkyl ethers; PtO_2–H_2SO_4 mediated reduction; Mitsunobu reaction.
* Corresponding author. Tel.: +1 908 740 2815; fax: +1 908 740 7152; e-mail: jianhua.chao@spcorp.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.161

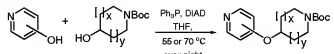


Scheme 1. General approach.

efficient approach to the formation of C–O bonds under nearly neutral conditions. Recent advances in this reaction have been reviewed by Dembinski.[6] The coupling of 4-hydroxy pyridine (**6a**), or 3-hydroxy pyridine (**6b**), with various hydroxy substituted *N*-heterocycles **7a–d** under the conditions of triphenyl phosphine (Ph_3P) and diisopropylazodicarboxylate (DIAD) afforded the desired pyridinyl ether products **5a–e** in good yields.[7] Although 4-hydroxy pyridine **6a** is predominantly in the pyridinone tautomer, we have observed that the Mitsunobu reaction proceeded only at the oxygen atom via the minor pyridine tautomer, similar to the tetrahydropyranylation results reported by Azzouz et al.[8] It is also worthy of mention that most of the phosphine oxide and hydrazine byproducts generated during this reaction were efficiently removed by taking advantage of the weakly basic pyridinyl nitrogen in **5** during an acidic work-up.[9] This procedure simplified the isolation process, and helped to avoid the usually time consuming removal of spent reagents from the Mitsunobu reaction. Table 1 summarizes the results of this transformation.

The conversion of the pyridinyl ethers **5** to the saturated ethers **4** was undoubtedly the key step of the sequence. Although reduction of a substituted pyridine to the corresponding piperidine is a common transformation,[10] often the pyridine ring requires activation with the presence of electron withdrawing groups or by the formation of the N-oxide. Without such activation, metal mediated hydrogenation requires high pressure and or high temperature. Initially, we have applied several common reductive methods, known to be effective for substituted pyridines, to the pyridinyl system **5**. Treatment of pyridinyl–piperidyl ether **5a** with samarium diiodide in THF–H_2O,[11] or lithium triethylborohydride in THF,[12] produced no reduction product. In order to activate the pyridinyl system, **5a** was oxidized to the corresponding N-oxide using *m*-chloroperoxybenzoic acid (*m*-CPBA).

Table 1. Preparation of pyridinyl ether **5**[a,9]



Entry	Hydroxy pyridine **6**	Alcohol **7**	Pyridyl ether **5**	Yield[c] (%)
1	**6a**	**7a**	**5a**	67
2[b]	**6b**	**7a**	**5b**	69
3	**6a**	**7b**	**5c**	80
4	**6a**	**7c**	**5d**	78
5	**6a**	**7d**	**5e**	69

[a] Reaction conditions: 1 mol equiv of hydroxy pyridine **6**, 1.25 mol equiv of alcohol **7**, 1.25 mol equiv of Ph_3P, 1.25 mol equiv of DIAD, and 0.3 M of THF, 55 °C, 14–16 h (over night).

[b] Reaction was carried out at 70 °C.

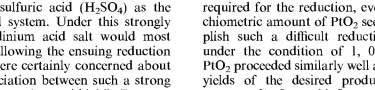
[c] Yields refer to purified products by column chromatography; purity was determined >95% based on LC-MS analysis.

The subsequent reduction of the N-oxide under the conditions of $HCOONH_4$/10% Pd–C in methanol[13] only generated the parent compound **5a**. The use of PtO_2 in MeOH–AcOH under a H_2 atmosphere was also proved to be ineffective even after employing a stoichiometric amount of PtO_2.

The above unsuccessful reduction attempts of **5a** strongly suggested that this electron rich pyridinyl system needed a much stronger activation in order to facilitate the desired reduction process. Weak acids similar to acetic acid would not be useful, and addition of electron withdrawing groups was not an option either. We decided to approach this in an unconventional way, by employing concentrated sulfuric acid (H_2SO_4) as the activator of the pyridinyl system. Under this strongly acidic condition, a pyridinium acid salt would most likely form in situ, thus allowing the ensuing reduction process to succeed. We were certainly concerned about the potential risk of association between such a strong acid with compounds like **5a** where acid labile Boc protecting group and ether linkage were present. However, we believed that under anhydrous conditions, one equivalent of concentrated sulfuric acid would preferably complex with the basic pyridinyl nitrogen. We were gratified to see that treatment of pyridinyl–piperidyl ether **5a** with the combination of PtO_2 (1 wt equiv) and H_2SO_4 (1 mol equiv) in ethanol under a H_2 atmosphere (maintained by a gas balloon) at room temperature afforded the reduced bicyclic ether product **4a**. The reaction was completed within a 10 h period. Following a facile work-up and column chromatography, ether product **4a** was obtained consistently above 50% on reaction scales ranging from 0.1 g to 1 g. The utility of this reduction process was extended to pyridinyl ethers **5b–e**, and the respective saturated ether products **4b–e** were obtained in good yields.

In order to investigate the possibility of a catalytic reduction process, we re-evaluated the amount of PtO_2 required for the reduction, even though initially a stoichiometric amount of PtO_2 seemed necessary to accomplish such a difficult reduction. Reductions of **5a–e** under the condition of 1, 0.5, and 0.25 wt equiv of PtO_2 proceeded similarly well and produced comparable yields of the desired products **4a–e**. However, the amount of PtO_2 used influences the duration of the reaction. Longer period of time was needed to ensure the complete consumption of the starting material when lesser amount of PtO_2 was employed. Results of the catalytic reduction of the pyridinyl ethers **5** are summarized in Table 2.[14]

Table 2. Catalytic reduction of pyridinyl ether **5** with PtO_2 in combination with H_2SO_4 or *p*TsOH–H_2O[a]



5 **4**

Entry	Pyridyl ether **5**	Bis-*N*-heterocyclic alkyl ether **2**	PtO_2[b] (0.25 equiv)	
			H_2SO_4	*p*TsOH
1	 **5a**	 **4a**	55% 14 h	60% 14 h
2	 **5b**	 **4b**	29% 14 h	28% 14 h
3	 **5c**	 **4c**	77% 18 h	NA[c]
4	 **5d**	 **4d**	61% 10 h	80% 20 h
5[d]	 **5e**	 **4e**	51% 20 h	NA[c]

[a] Reaction conditions: all reactions were performed on a 1.0 g scale of pyridinyl ether **5**, 0.25 wt equiv of PtO_2, 1.0 mol equiv of H_2SO_4 or 1.0 mol equiv of *p*TsOH–H_2O, 200 proof ethanol (20 mL), H_2 supplied by a gas balloon.

[b] Yields refer to purified ether products **2** by column chromatography, purity >95% based on LC-MS analysis.

[c] NA means reaction was not performed.

[d] A 0.5 wt equiv of PtO_2 was used.

The bis-*N*-heterocyclic ethers **4** were obtained in moderate to good yields, as illustrated in Table 2, based on the current un-optimized conditions. During the reduction process, we did observe the formation of byproducts consistent with the cleavage of the ether link and the removal of the Boc protection, based on TLC and MS analysis. Byproducts resulting from ether link cleavage were isolated and confirmed to be hydroxy *N*-heterocycles **7** based on H NMR. Additionally, the amount of byproducts formed seems to be substrate dependent. In an effort to minimize the acid induced side reactions, *p*-toluenesulfonic acid was evaluated as a possible alternative. It was found that *p*-toluenesulfonic acid was equivalent to concentrated sulfuric acid in the catalytic reduction of **5a**, **5b**, **5d** (Table 2), but unfortunately byproducts were generated at a similar level as those of the reactions mediated by concentrated sulfuric acid.

In summary, we have reported here a two-step sequence for the synthesis of previously inaccessible mono-Boc-protected bis-*N*-heterocyclic alkyl substituted ethers **4a**–**e**. The reduction of electron rich pyridinyl system was realized with the combination of PtO_2–H_2SO_4 (or *p*TsOH). Furthermore, the reduction can be carried out catalytically. The ethers **4a**–**e** thus prepared have become versatile building blocks in our SAR development being further elaborated into biologically important chemical entities.

Acknowledgments

We thank Drs. John Piwinski, Robert Aslanian, and Alan Cooper from SPRI, Dr. Kenneth Yamaguchi and Mr. Ronald Paige from NJCU for their support of the special SPRI-NJCU Corporate Scholar program which made Ms. Israiel's summer internship possible.

Supplementary data

Experimental procedures, characterization data, and NMR spectra for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.161.

References and notes

1. Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1702–1729.
2. Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379–423.
3. Arai, H.; Matsumura, T.; Ishida, H.; Yamaura, Y.; Aratake, S.; Ohshima, E.; Yanagawa, K.; Miyama, M.; Suzuki, K.; Kawabe, A.; Nakanishi, S.; Kobayashi, K.; Sato, T.; Miki, I.; Ueno, K.; Fujii, S.; Iwase, M. WO 2003104230 A1, 2003, 467 pp.
4. Bailey, J. M.; Burton, G.; Huxley, A.; Milner, P. H.; Orlek, B. S. WO 2005/014571 A1, 2005, 72 pp.
5. Mitsunobu, O. *Synthesis* **1981**, 1–28.
6. Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763–2772.
7. For O-alkylation of 3-hydroxy pyridine under Ph_3P/DEAD condition, see: (a) Dolle, F.; Dolci, L.; Valette, H.; Hinnen, F.; Vaufrey, F.; Guenther, I.; Fuseau, C.; Coulon, C.; Bottlaender, M.; Crouzel, C. *J. Med. Chem.* **1999**, *42*, 2251–2259, and references cited therein; (b) We did not pursue the coupling reaction of 2-hydroxy pyridine and **7a** under the discussed Mitsunobu protocol since the fully saturated bis-*N*-heterocyclic alkyl ether was considered unsuitable for our SAR purpose. However, O-alkylation of 2-hydroxy pyridine under Mitsunobu condition might be possible, see Ref. 8 for details.
8. Azzouz, R.; Bischoff, L.; Fouquet, M.-H.; Marsais, F. *Synlett* **2005**, *18*, 2808–2810.
9. General procedure for the preparation of pyridyl ethers **5**: To a stirred solution of 4-hydroxy pyridine **6a** (2.0 g, 21.03 mmol) in 70 mL of anhydrous THF at room temperature was added *N*-Boc-4-hydroxy piperidine **7a** (5.3 g, 26.28 mmol). Triphenyl phosphine (6.9 g, 26.31 mmol) was added followed by dropwise addition of diisopropylazodicarboxylate (DIAD, 5.2 mL, 26.41 mmol). The mixture was heated at 55 °C over night (14 h). Solvent was evaporated in vacuo. The resulting oil was treated with a 1.0 M HCl aqueous solution (30 mL). The acidic mixture was washed with CH_2Cl_2 (30 mL × 2). The combined CH_2Cl_2 washings were re-extracted with a 1.0 M HCl aqueous solution (10 mL) and H_2O (20 mL), then discarded. The aqueous fractions were combined, basified to pH ~ 12 using a 1.0 M NaOH aqueous solution, and extracted with CH_2Cl_2 (50 mL × 4). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to a residue, which was purified by flash column chromatography, eluting with EtOAc–hexanes–MeOH (5:1:0.1, v/v/v). Removal of solvents afforded 3.92 g (67%) of pyridyl ethers **5a** as a colorless solid.
10. (a) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1990; (b) Glorius, F.; Spielkamp, N.; Holle, S.; Goddard, R.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2850–2852.
11. Kamochi, Y.; Kudo, T. *Heterocycles* **1993**, *36*, 2382–2396.
12. Blough, B. E.; Carroll, F. I. *Tetrahedron Lett.* **1993**, *34*, 7239–7242.
13. Zacharie, B.; Moreau, N.; Dockendorff, C. *J. Org. Chem.* **2001**, *66*, 5264–5265.
14. General procedure for bis-*N*-heterocyclic alkyl ethers **4**: A stirred solution of pyridyl ether **5a** (1.0 g, 3.6 mmol) in 20 mL of 200 proof ethanol was degassed via house vacuum, and refilled with nitrogen. PtO_2 (0.25 wt equiv) was added. The mixture was degassed again and refilled with nitrogen. Concentrated sulfuric acid (0.19 mL, 3.6 mmol, 1 equiv) was added. The resulting mixture was degassed a third time, and refilled with H_2 via a stainless needle connected to a gas balloon. Reaction was continued at room temperature under a H_2 atmosphere for 14 h. The mixture was poured into 50 mL of an ice cold 1.0 M NaOH aqueous solution, rinsing with a small volume of CH_2Cl_2, and filtered through a Celite® pad. The filtrate was concentrated in vacuo to remove ethanol, and the remaining aqueous solution was extracted with CH_2Cl_2 (50 mL × 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to an oily residue, which was purified by flash column chromatography, eluting with CH_2Cl_2–MeOH (10:1, 5:1, and 1:1, v/v). Removal of solvents afforded 0.61 g (60%) of ether **4a** as a colorless solid.